REMARKS

The Amendments

In order to advance prosecution, Applicants have amended claim 1 and dependent claims 2-31. Specifically, claim 1 has been amended to recite a chemically synthesized double stranded short interfering RNA (siRNA) molecule that directs cleavage of a huntingtin (HD) RNA comprising SEQ ID NO:3578 via RNA interference, wherein: each strand of said siRNA molecule is about 18 to about 27 nucleotides in length; one strand of said siRNA molecule comprises nucleotide sequence having sufficient complementarity to said HD RNA for the siRNA molecule to direct cleavage of the HD RNA via RNA interference; and one or more pyrimidine nucleotides present one or both strands of said siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide. Support can be found in the specification, *inter alia*, at for example, pages 9, lines 11-26; page 18, lines 10-27; page 34, lines 22-27; page 69, line 10 to page 72, line 7; and page 142, (see entry for GenBank entry NM_002111, Table I). Claims 1-31 have been amended to recite the term "siRNA" rather than "siNA". Support for the amendment can be found *inter alia*, at for example, page 69, line 10 to page 72, line 7 and throughout the specification.

Amendments to the claims are made without prejudice and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicant reserves the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a new sequence listing and request its entry in place of the previously entered sequence listing. The sequence listing adds SEQ ID NO: 3578. The sequence represents GenBank entry NM_002111 (see Tables I and II). The version of NM_002111 appearing in the sequence listing as SEQ ID NO: 3578 appeared in GenBank on October 31, 2000. Applicant submits that the CD-R submitted in lieu of the paper copy and the

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CD-R submitted for the computer-readable copy are identical in content. The sequence listing adds no new matter and applicants respectfully request its entry.

Rejection of Claims Under 35 U.S.C. § 112, second paragraph

Claim 18 stands rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention because it is unclear where the claim ends because the claim does not end with a period. Claim 18 has been amended to include a period at the end of the claim. Applicant respectfully requests withdrawal of the 35 U.S.C. §112, second paragraph, rejection.

Rejection of Claims Under 35 U.S.C. § 112, first paragraph

Claims 1-31 stand rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse the rejection.

The Office Action asserts that although the specification as filed discloses siNA sequences having complementarity to HD, the specification does not provide information regarding siNA molecules directed to any other species of HD polynucleotides to describe the instantly claimed genus of siNA molecules directed to any HD gene. The Office Action concludes that the skilled artisan would not be able to envisage the entire genus claimed of siNA molecules that would direct cleavage of any HD RNA. Applicants respectfully disagree with this argument because the specification as filed discloses siNA molecules targeting mutant HD sequences, HD polymorphisms, and various other HD genes (see for example page 8, line 12 to page 9, line 2). In addition, the definition of the term "HD", referring to "nucleic acid sequences encloding any huntingtin protein, peptide, or polypeptide, such as Huntingtin RNA or Huntingtin DNA (see for example Van Dellen *et al.*, January 24, 2004, Neurogenetics)" and the terms "target" and "target gene" includes a broad description of target HD sequences (see for example page 73, line 28 to page 74, line 31). The specification also discloses a large representative number of various HD sequences referred to by GenBank Accession number, see for example Table 1 beginning on page 142. The specification also discloses a comprehensive set of HD polymorphic variants and corresponding siNA constructs in Table II. It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a

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generic invention. *Capon v. Eshhar*, 418 F.3d 1349, 1360 (Fed. Cir. 2005). Therefore, contrary to the assertions of the Office Action, the application provides sufficient basis for the claimed genus of siNA molecules that would direct cleavage of any HD RNA.

However, in the interest of expediting prosecution, claim 1 has been amended to recite siRNA molecules having complementarity to SEQ ID NO:3578, referring to GenBank accession No. NM_002111 for human HD RNA. Thus, the claims as amended are directed to siRNAs that target one species of HD RNA.

Under 35 U.S.C. § 112, first paragraph, all that is required to satisfy the written description requirement is that the specification describe the claimed invention in sufficient detail such that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306 (Fed. Cir. 2003); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991); M.P.E.P § 2163(I). Possession is shown "by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." M.P.E.P. § 2163.02 (citing *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir.1997)).

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. M.P.E.P. § 2163(I)(A) (citing *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976)). Thus, a description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. *See, e.g., In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971); M.P.E.P. § 2163.04. Therefore, the Office must have a reasonable basis to challenge the adequacy of the written description and has the initial burden of presenting, by a preponderance of the evidence, why a person skilled in the art would not recognize in an Applicant's disclosure a description of the invention defined by the claims. *See, e.g., In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976); M.P.E.P. § 2163.04.

Whether the specification shows that an applicant was in possession of the claimed invention is a factual determination. M.P.E.P. § 2163(I). Factors to be considered in determining whether there is sufficient evidence of possession include: (1) the level of skill and

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knowledge in the art; (2) partial structure; (3) physical and/or chemical properties; (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function; and (5) the method of making the claimed invention. *Id.* at (II)(A)(2)-(3)(a). Disclosure of *any* combination of such identifying characteristics that distinguish the claimed invention such that one skilled in the art would conclude that the applicant was in possession of the claimed species is sufficient. *Id*; *see Reagents of the Univ. of Calif. v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Contrary to the Office's allegation, the specification fully describes the claimed double stranded nucleic acid molecules in sufficient detail such that one skilled in the art would reasonably conclude that applicants had possession of the claimed invention. For example, the specification teaches the structure, function, and properties of the target HD gene (specification at, for example, pages 122-124). Importantly, the specification provides the sequence of **numerous** exemplary HD target nucleic acid sequences (see HD sequences referred to by Genbank Accession numbers listed in Table I) and further teaches that the HD target includes other HD encoding sequences, such as other HD isoforms, mutant HD genes, splice variants of HD genes, and HD gene polymorphisms (see pages 8, 10, and 54).

In addition, the specification teaches the structure and chemical properties of the claimed double stranded nucleic acid molecules. First, the specification teaches that the double stranded nucleic acid molecule comprises a sense strand and an antisense strand (specification at, for example, pages 10-12, 21-25, and 70). The antisense strand comprises sequence complementary to human HD nucleotide sequence (which HD sequence is taught as discussed above). The sense strand comprises sequence complementary to the antisense strand. The specification further teaches that the size of the double stranded nucleic acid molecules is 18 to about 27 nucleotides in length (specification at, for example, pages 21, 22, and 34). Importantly, the specification teaches the structure, i.e., sequence, of **thousands** of representative examples of the claimed double stranded nucleic acid molecules (see Table II). In addition, the specification teaches that the double stranded nucleic acid molecules can be chemically modified and teaches **numerous** examples of various types of chemical modifications (specification at, for example, pages 13-49 and 99-108) and provides **numerous** examples of chemically modified double stranded nucleic acid molecules (see Table III and Figures 4 and 5).

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In addition to teaching the structural, chemical, and physical properties of the claimed double stranded nucleic acid molecules, the specification teaches the functional characteristics of the claimed double stranded nucleic acid molecules, namely to modulate the expression of HD gene (specification at, for example, pages 49-54).

Finally, the specification teaches methods of making the claimed double stranded nucleic acid molecules (specification at, for example, pages 95-99, 124-126, and 130-132) and methods of testing the activity of the double stranded nucleic acid molecules (specification at, for example, pages 132-136). The specification also teaches the administrating the claimed double stranded nucleic acid molecules (specification at, for example, pages 108-122) and several uses of the double stranded nucleic acid molecules (specification at, for example, pages 137-139).

Thus, the specification teaches virtually **ALL** of the characteristics listed in MPEP 2163(II)(A)(2)-(3)(a) used to demonstrate possession of the invention, as well as additional characteristics.

Despite the teachings and examples provided in the specification, the Office alleges that the applicants have not shown possession of the invention. In making the argument, the Office appears to allege that an applicant does not show possession unless he or she has reduced the invention to practice. However, applicants submit that the written description requirement does not require an actual reduction to practice. MPEP 2163 (II)(A)(3)(a). Thus, an applicant does not have to include a working example to satisfy the written description requirement. Regardless, applicants refer to Example 9 and Figure 30 which were filed with the corresponding continuation application USSN 11/063415, filed February 22, 2005. Example 9 and Figure 30 describe and show the results of experiments performed to test the activity of several of the double stranded nucleic acid molecules described in Table III of the instant application (see page 195). As explained in Example 9 and Figure 30, applicants tested the activity of double stranded nucleic acid molecules 31993/31994, 31995/31996 (chemically modified), and 31997/31998 (chemically modified) in HEK-293 cells and found that each of them inhibits the human HD target as compared with inverted matched chemistry control nucleic acid molecules.

Applicants have demonstrated possession of the claimed invention by providing the structure and chemistry of numerous representative examples of double stranded nucleic acid

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molecules that target HD (throughout the entire specification and in the Tables) and by demonstrating that exemplary double stranded nucleic acid molecules target and inhibit human HD.

For the reasons stated above, Applicant respectfully requests withdrawal of the 35 U.S.C. §112, first paragraph, rejection.

Priority

The Office Action alleges that the instant application is not entitled to priority to International Patent Application PCT/US03/05028 and U.S. Provisional Applications 60/358,580, 60/363,124, 60/386,782, 60/406,784, 60/408,378, 60/409,293, and 60/440,129. The Applicant respectfully disagrees.

The present application claims priority to, *inter alia*, 60/363,124 (the '124 application), filed March 11, 2002. The claims presented above all find support in, *inter alia*, the '124 application. The Office specifically alleges that although the prior applications disclose siNA molecules, they fail to discuss a siNA molecule that targets HD RNA. However, the '124 application teaches siNA molecules targeted to HD RNA in Table III of the application (entry in Table III for GenBank Accession No. NM_002111). Furthermore, in particular, amended claim 1 finds support for chemically synthesized double-stranded nucleic acid molecule at p. 3, lines 15-17; p. 32, lines 11-12; p. 35, lines 29-30, and p. 60, line 20; complementarity between the first and second strands at p. 12, lines 4-7, p. 19, lines 11-14, p. 20, lines 16-20, p. 21, lines 3-6, and p. 25, lines 17-29; one strand having between 18-27 nucleotides complementary to human HD nucleic acid sequence at p. 18, lines 1-5, p. 12, line 6, p. 372, entry in Table III for GenBank Accession No. NM_002111; and at least two different modified nucleotides at p. 5, line 13 to page 15, line 9, and p. 36, line 1 to page 37 line 31. Therefore, the instant application is entitled to a priority date of at least March 11, 2002, the filing date of the 60/363,124 application.

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Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-9, 13-15, and 18-31 stand rejected as allegedly obvious over Hayden *et al.* (US 2002/0187931), in view of Davidson *et al.* (US 2004/0241854), Tuschl *et al.* (WO 02/44321), Elbashir *et al.*, 2001, EMBO J., 20:6877-6888, Parrish *et al.* 2000, *Molecular Cell*, 6:1077-1087, and Morrissey *et al.* (U.S. Publ. No. 2003/0206887 A1). Applicants respectfully traverse the rejections.

Applicant submits that Davidson et al. and Morrissey et al. are not proper prior art references. Davidson et al. was filed on December 16, 2003, with priority claimed to August 5, 2002, both of which dates are after the effective filing date of the present invention (see discussion of priority above). Morrissey is improper 102(e) art for the purposes of 35 U.S.C. 103(a) because the inventors of the Morrissey *et al.* application were under an obligation of assignment to Sirna Therapeutics Inc. at the time the present application was filed. Thus, the present invention and the Morrissey et al. application were under obligation of common assignment at the time the present invention was made.

In the interest of advancing prosecution, claim 1 has been amended to recite a chemically synthesized double stranded short interfering RNA (siRNA) molecule that directs cleavage of a huntingtin (HD) RNA comprising SEQ ID NO:3578 via RNA interference, wherein: each strand of said siRNA molecule is about 18 to about 27 nucleotides in length; one strand of said siRNA molecule comprises nucleotide sequence having sufficient complementarity to said HD RNA for the siRNA molecule to direct cleavage of the HD RNA via RNA interference; and one or more pyrimidine nucleotides present one or both strands of said siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide.

Applicants submit that the Office Action has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP §2143.

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Here, the knowledge of one of ordinary skill prevented the inventions claimed in the instant application from being realized. There is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

An examiner can satisfy the burden required for obviousness in light of combination "only by showing some objective teaching [leading to the combination]." *See, In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). Evidence of the teaching or suggestion is "essential" to avoid hindsight. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir.1988). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *See, e.g.*, *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985). "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 U.S.P.Q.2d 1635, 1637 (Fed. Cir. 1998). The need for specificity is important. *See, e.g., In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1317(Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed").

Hayden et al. teach that antisense oligonucleotides can target the cellular gene or mRNA transcribed from that gene that encodes the huntingtin protein. Elbashir (*Genes and Development*, 2001) describes chemically synthesized siRNA duplexes with overhanging 3'-ends that mediate RNAi in Drosophila embryonic lysate. Tuschl teaches nothing more than what is described in Elbashir (authors of Elbashir are co-inventors on Tuschl). Parrish reports that

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duplexes only as short as 26 bp can trigger RNA. Parrish also deals with a non-mammalian system, *C. elegans*. Significantly, Parrish reports that dsRNA triggers having 14 and 23 uninterrupted nucleotide identity to the target induced **no** interference. P. 1079, right col. Parrish does show that certain chemical modifications are tolerated in long (742 nucleotide long) double stranded RNA constructs (e.g., 2'-aminouridine, 2'-deoxythymidine, 2'-fluorouridine or 5-iodouridine). Neither Parrish nor Elbashir teach or suggest HD as a target for RNA interference using **short** interfering nucleic acids.

The Office Action alleges that it would have been obvious to one of ordinary skill in the art to specifically target a siRNA to a HD gene, since Hayden et al. teach antisense inhibition of HD and Tuschl et al. teach that siRNAs are new alternatives to antisense oligonucleotides because both antisense oligonucleotides and siRNA duplexes are both sequence specific inhibitors of target gene expression. The Office Action also alleges that it would have been obvious to one of ordinary skill at the time of the invention was made to incorporate modifications as taught by Parrish *et al.* and Tuschl *et al.* The Examiner's position goes no further than suggesting that it would have been obvious to try the chemical modifications previously used in connection with long double stranded RNA as taught by Parrish and antisense as taught by Hayden. Without acquiescing to the position, even if it were true, such position is not the correct standard for judging non-obviousness. Moreover, the subsequent prior art, including Elbashir and Tuschl, establishes that such suggestions failed in relation to siRNA technology, and this was the status of understanding in the art as of the time of the present invention.

One of skill in the art would not have been motivated to combine the cited references to arrive at the presently claimed invention. Elbashir (*EMBO J*, 2001) and Tuschl are the only references cited that teach a structure of the claimed nucleic acid molecules, *i.e.*, a short double stranded RNA molecule having one strand complementary to a target RNA and another strand having sequence comprising a portion of the target RNA sequence. Parrish teach longer dsRNA constructs and was published before the discovery of short interfering RNA. The teachings of Hayden deal with antisense technology. Although antisense is a nucleic acid based technology, it differs substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to

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remain active. Just as antisense modifications are not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs described by Elbashir (*EMBO J*, 2001).

In addition, the teachings of Parrish for modification of long double stranded RNA did not provide guidance to chemical modification of short interfering RNA. For example, Elbashir, in a previous publication (*Genes and Development*, 2001) references the work of Parrish by noting "in *C. elegans* that certain chemical modifications (e.g., 2'-aminouridine, 2'-deoxythymidine, or 5-iodouridine) incorporated into dsRNA are well tolerated at the sense, but not the cleavage-guiding antisense, strand." (see Elbashir *Genes and Development*, 2001, p 198) (Elbashir 1). Elbashir in the later publication cited in the Office Action (Elbashir, 2001, *EMBO Journal*, 20:6877-6888) (Elbashir 2) and Tuschl attempted to apply chemical modifications to siRNA based on the teachings of the prior art (e.g., Parrish) but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. These molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. For example, the discussion of pages 6881 and 6882 of Elbashir 2 (also in Tuschl, page 46) describes 2'-deoxy and 2'-O-methyl modified siRNA duplexes and is reproduced below:

> To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of the siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.

Figure 4 of Elbashir 2 (same as Figure 14 in Tuschl) clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Importantly, in all cases where 2'-O-methyl substitutions were used, this modification was shown not to be tolerated for RNAi. In addition, according to "*The siRNA Users Guide*" on page 6885 of Elbashir 2 (Tuschl Pages 49-50),

> 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes. More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of

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siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.

Therefore, the 2'-deoxy modification, which was taught by Parrish to be tolerated in long double stranded RNAs (*see,* Parrish, page 1081 and Figure 5), was not tolerated in short double stranded RNAs. As such, those of ordinary skill in the art would have understood that short double stranded RNAs were not amenable to the chemical modifications taught by Parrish for long double stranded RNAs.

Based on the teachings of "[t]he siRNA Users Guide" from Elbashir-2 and Tuschl, for example, one of skill in the art would not have been motivated to make any modifications beyond the 2'-deoxynucleotide substitutions at the 3'-end of the siRNA molecule and certainly would not be motivated to pursue the presently claimed invention. This is further evident from the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Elbashir 2 and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA (*see, e.g.,* Bitko *et al.,* 2001, BMC Microbiology, 1, 34 page 9, left column under heading Materials and Methods section; Kumar *et al.*, 2002, Malaria Journal, 1:5, page 9, right column, under heading Transfection by Inhibitory dsRNA"; Holen *et al.,* 2002, Nucleic Acids Research, 30, 1757-1766, Figures 1, 2 and 6). These prior art references represent the state of the art at the time and demonstrate that Elbashir and Tuschl taught away from the presently claimed invention

Further, a plain reading of Elbashir 2 teaches that 2'-*O*-methyl modifications are not tolerated and likely interfere with protein association in siRNP assembly. As such, neither Parrish, Elbashir nor Tuschl provide any motivation to a person skilled in the art to take the teachings of long dsRNA, antisense or ribozymes and apply it to double stranded RNA molecules as presently claimed, because Elbashir and Tuschl tried this approach and failed; Elbashir and Tuschl therefore teach away from using modifications beyond use of 2'-deoxynucleotides at the 3'-terminal positions of the double stranded RNA molecules. Thus, one of skill in the art would not have been motivated to selectively incorporate one or more 2'-deoxy-2'-fluoro modifications at pyrimidine positions within the double stranded RNA molecules as required by the presently claimed siRNA molecules.

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The applicants were the first to show that selective incorporation of 2'-deoxy-2'-fluoro modifications at pyrimidine positions are well tolerated in double stranded nucleic acid molecules targeting gene expression, as evidenced by the fact that the applicants were the first to utilize double stranded nucleic acid molecules as presently claimed to successfully down regulate gene expression. In the instant application, the claimed siRNA molecules were used to successfully target a human huntingtin sequence as is presently claimed, see Figure 22 which shows that siNA constructs with 2'-deoxy-2'-fluoro pyrimidine modifications (SEQ ID NOS:3514/3515 and 3516/3517) demonstrate inhibition of HD82Q-myc compared with inverted matched chemistry siRNA constructs. Furthermore, the active siNA constructs showed selectivity for inhibiting the myc tagged HD82Q compared to c-myc and the necomycin transfection control (see description of Figure 22 on page 92 and in Example 9 on pages 136-137). Moreover, in co-pending application USSN 10/444,853, published as US-2004-0192626, applicant designed, synthesized, and tested several 2'-deoxy-2'-fluoro pyrimidine modified double stranded nucleic acid molecules having potent activity directed against several different gene targets (see for example Figure 6 with a corresponding description on page 28, paragraph [0219], Figure 7, with a corresponding description on page 28, paragraph [0220], both described in Example 5 starting on page 68 and with sequences shown in Table I; see also Figures 11-15). These co-pending applications of Applicant are the first to demonstrate that application of 2'-deoxy-2'-fluoro pyrimidine modifications to double stranded nucleic acid structures are well tolerated for maintaining potent RNAi activity against HD and other target nucleic acid sequences.

Based on the state of the art at the time of filing (which taught away from siRNA having the recited chemical modifications) and for the reasons provided above, a person skilled in the art would not have been motivated to follow the teachings of Parrish, Elbashir, or Tuschl, let alone the antisense or ribozyme art, to make and use the double stranded nucleic acid molecules of the present invention to target human huntingtin gene expression.

Moreover, the cited references, alone or in combination, do not provide a reasonable expectation of success. The existence or lack of a reasonable expectation of success is assessed from the perspective of a person of ordinary skill in the art at the time the invention was made. *See, Micro Chem. Inc. v. Great Plains Chem. Co.,* 103 F.3d 1538, 1547, 41 U.S.P.Q.2d 1236,

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1245 (Fed. Cir. 1997). The inventors' ultimate success is irrelevant to whether one of ordinary skill in the art, at the time the invention was made, would have reasonably expected success. *See, Standard Oil Co. v. American Cyanamid Co*, 774 F.2d 448, 454, 227 U.S.P.Q. 293, 297 (Fed. Cir. 1985). It is impermissible to use hindsight. That is, using the inventors' success as evidence that the success would have been expected. *See, In re Kotzab*, 217 F.3d 1365, 1369, 55 U.S.P.Q.2d 1313, 1316, (Fed. Cir. 2000). Applicant submits that no prima facie case of obviousness exists because, as described above, there would be no motivation to combine the cited references, no reasonable expectation of success in such a combination, and finally, the cited references in combination do not properly teach the presently claimed invention, and in fact, teach against the instant claims. Because no prima facie case of obviousness has been established, the applicant's respectfully submit that the Office has used improper hindsight reasoning in rejecting the claims. Clarification of the claims by virtue of the present amendments further obviates the rejection.

For the reasons set forth above, namely that Davidson et al and Morrissey et al. are not proper prior art and that Hayden *et al.* (US 2002/0187931), in view of Tuschl *et al.* (WO 02/44321), Elbashir *et al.*, 2001, EMBO J., 20:6877-6888, and Parrish *et al.* 2000, *Molecular Cell*, 6:1077-1087 do not teach or suggest making a chemically synthesized double stranded short interfering RNA (siRNA) molecule that directs cleavage of a huntingtin (HD) RNA comprising SEQ ID NO:3578 via RNA interference, wherein: each strand of said siRNA molecule is about 18 to about 27 nucleotides in length; one strand of said siRNA molecule comprises nucleotide sequence having sufficient complementarity to said HD RNA for the siRNA molecule to direct cleavage of the HD RNA via RNA interference; and one or more pyrimidine nucleotides present one or both strands of said siRNA molecule is a 2'-deoxy-2'-fluoro pyrimidine nucleotide with a reasonable expectation of success. Therefore, because there would be no motivation to combine the cited references, because there would be no reasonable expectation of success in such a combination, and because the cited references in combination do not even teach the presently claimed invention, the cited references do not render the present invention obvious. Accordingly, Applicant respectfully requests withdrawal of these 35 U.S.C. § 103(a) rejections.

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Claims 1, 6, 10-12, and 17 stand rejected as allegedly obvious over Hayden *et al.* (US 2002/0187931), in view of Tuschl *et al.* (WO 02/44321) and Matulic-Adamic *et al.* (U.S. 5,998,203). Applicants respectfully traverse the rejections.

The Office Action relies on the teachings of Hayden et al and Tuschl et al. to establish the obviousness of targeting a modified siRNA duplex to a huntingtin gene. The Office Action further alleges that Matulic-Adamic teaches the use of 5' and 3' caps to prevent nuclease degradation of enzymatic nucleic acid molecules and also teaches the use of base, sugar, and/or phosphate modifications to enzymatic nucleic acid molecules. The Office Action alleges that it would have been obvious to one of ordinary skill to incorporate modifications as taught by Matulic Adamic *et al.* into a siRNA duplex targeted to an HD gene to arrive at the presently claimed invention.

First, for the reasons stated above, Hayden et al and Tuschl et al. do not teach the presently claimed siRNA molecules. Specifically, the present claims require the selective incorporation of 2'-deoxy-2'-fluoro modification at one or more pyrimidine nucleotides in one or both strands of the siRNA molecule targeted to HD RNA. For the previously stated reasons, neither Hayden, nor Tuschl teach or suggest such modification as applied to siRNA molecules with a reasonable expectation of success.

The Matulic Adamic *et al.* reference fails to cure the deficiencies of Hayden in view of Tuschl. Although Matulic Adamic *et al.* teach generally the use of sugar modifications to ribozyme molecules, Matulic Adamic *et al.* fail to teach or suggest the selective incorporation of 2'-deoxy-2'-fluoro modification at one or more pyrimidine nucleotides, much less such modification in one or both strands of siRNA molecules. Furthermore, the teachings of Matulic Adamic *et al.* deal with ribozyme technology. Although ribozyme technology is a nucleic acid based technology, it differs substantially from the present invention both mechanistically and structurally, particularly in relation to the chemical modification strategies that allow such molecules to remain active. Just as antisense modifications are not amenable to ribozymes and vice versa, neither of these nucleic acid technologies provides any insight or guidance into chemical modification of the siRNAs described by Tuschl.

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The Office Action further alleges that one skilled in the art would have a reasonable expectation of success based on the combined references because "each of the modifications were known in the art to benefit ribozymes, as taught by Matulic-Adamic et al. Therefore, one would reasonably expect the same benefits to a siRNA molecule". (Office Action, page 11). However, the Office provides no further explanation or evidence to demonstrate the basis for the naked assertion that "one would reasonably expect the same benefits to a siRNA molecule".

In the absence of such evidence, the Examiner's position goes no further than suggesting that it would have been obvious to try the chemical modifications previously used in connection with ribozymes as taught my Matulic-Adamic. However, this is not the correct standard for judging obviousness.

Furthermore, in fact, given the state of the art at the time of filing, one would **not** have reasonably expected the same benefits of modification to a siRNA molecule. As discussed above, Tuschl attempted to apply chemical modifications to siRNA based on the teachings of the prior art, such as those modifications taught in Matulic Adamic *et al.*, but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. As previously explained, Tuschl's siRNA molecules having internal 2'-deoxy substitutions were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. Tuschl's findings were the accepted state of the art at the time of filing, as evidenced by the publications in the field around 2001 and 2002, where experts in the field followed the teachings of Tuschl and designed siRNAs without any modifications other than two deoxythymidine nucleotides at the 3'-end of the siRNA. Thus, one skilled in the art would not have had a reasonable expectation that the modifications described in Matulic Adamic *et al* could be successfully applied to siRNA molecules.

For the reasons set forth above, Hayden *et al.* (US 2002/0187931), in view of Tuschl *et al.* (WO 02/44321) and Matulic-Adamic *et al.* (U.S. 5,998,203) do not render obvious the presently claimed invention. Accordingly, Applicant respectfully requests withdrawal of these 35 U.S.C. § 103(a) rejections.

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Rejection of Claims Under Judicially Created Doctrine of Obviousness-Type Double Patenting

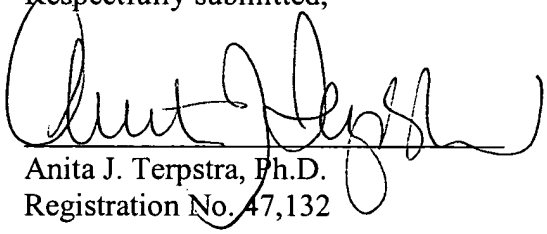
Claims 1-31 stand as provisionally rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Appl. No. 10/783,128.

While not in agreement with the Office Action on this rejection, Applicants, in the interest of efficient prosecution of this application, will consider submitting a terminal disclaimer over U.S. Appl. No. 10/783,128 upon indication of allowable claims in the instant application.

Conclusion

In view of the foregoing amendments and remarks, the applicant submits that the claims are in condition for allowance, which is respectfully solicited. If the examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned as indicated below.

Respectfully submitted,



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